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Inventor(s): (72)

Werner Aschwanden, Ettingen; Dr. René Imhof, Gipf-Oberfrick, CH [Switzerland]; Dr. Roland Jakob-Roetne, Inzlingen, DE [Germany]; Dr. Emilio Kyburz, Reinach, CH

Patent holder: (71)

F. Hoffmann-La Roche et CO., AG, Basel, CH

Procedure for Producing Cinnamic Acid Derivatives and Pharmaceutical Preparations Containing Such Agents

(57) ABSTRACT

New cinnamic acid derivatives of general formula (1), (in which formula,

among R^1, R^2, R^3 and R^4, one or two represent a halogen atom or a methoxy group and the others represent a hydrogen atom;

R^5 is a hydrogen atom or a phenyl group,

R^6 is a group of general formula $-OR^{12}$ (a) or $-NR^{13}R^{14}$ (b),

R^7 is a 1-4 carbon atom alkyl group, a 2-5 carbon atom alkanoyl-amino-(2-5 carbon atom alkyl) group, an amino group or an alkoxyphenyl group with 1-4 carbon atoms,

R^8 and R^9 are a hydrogen atom or a 1-4 carbon atom alkyl group,

R^{10} is a hydrogen atom and R^{11} is a hydroxyl group or

R^{10} and R^{11} together are an oxo group,

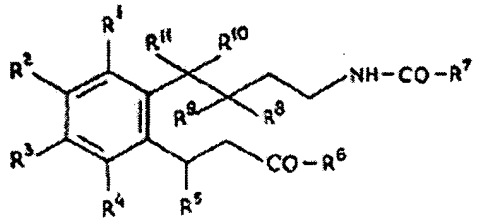
R^{12} is a hydrogen atom, an alkyl group with 1-10 carbon atoms, a pyridylmethyl or carbamoyl-methyl group,

R^{13} is a hydrogen atom or an alkyl group with 1-4 carbon atoms,

R^{14} is a hydrogen atom, a 1-4 carbon atom alkyl group, a pyridyl group, a phenyl-(1-4 carbon atom alkyl)- group, a carboxy-(1-4 carbon atom alkyl)-group, a carbamoyl-(1-4 carbon atom alkyl)- group, a 1-4 carbon atom alkoxy*-carbonyl-(1-4 carbon atom alkyl)-group, a di-(1-4 carbon atom alkoxy-(carbonyl-)2-5 carbon atom alkyl)- group, a piperidinyl-(2-4 carbon atom alkyl)- group or a halogen-pyridino-carboxamido-(2-4 carbon atom alkyl)- group [* *Hungarian 'akoxi' should be 'alkoxi'*] or

R^{13} and R^{14}, together with an adjacent nitrogen atom to which they are attached, form a 4-(1-4 carbon atom alkyl)-piperazin-1-yl group)

may be used to treat or prevent brain insufficiency and improve cognitive functions.



(I)

The invention relates to the preparation of new cinnamic acid derivatives. More specifically, the object of the invention is cinnamic acid derivatives of general formula (I)
(in which formula,
among R^1, R^2, R^3 and R^4, one or two represent a halogen atom or a methoxy group and the others represent a hydrogen atom;
R^5 is a hydrogen atom or a phenyl group,
R^6 is a group of general formula $-OR^{12}$ (a) or $-NR^{13}R^{14}$ (b),
R^7 is a 1-4 carbon atom alkyl- group, a 2-5 carbon atom alkanoyl-amino-(2-5 carbon atom alkyl)- group, an amino group or a 1-4 carbon atom alkoxy-phenyl group,
R^8 and R^9 are a hydrogen atom or an alkyl group with 1-4 carbon atoms,
R^{10} is a hydrogen atom and R^{11} is a hydroxyl group or
R^{10} and R^{11} together are an oxo group,
R^{12} is a hydrogen atom, a 1-10 carbon atom alkyl group, a pyridylmethyl or carbamoyl-methyl group,
R^{14} is a hydrogen atom, a 1-4 carbon atom alkyl group, a pyridyl group, a phenyl-(1-4 carbon atom alkyl)- group, a carboxy-(1-4 carbon atom alkyl)- group, a carbamoyl-(1-4 carbon atom alkyl)- group, a 1-4 carbon atom alkoxy-carbonyl-(1-4 carbon atom alkyl)- group, a di-(1-4 carbon atom alkoxy)-carbonyl-(2-5 carbon atom alkyl)- group, a piperidino-(2-4 carbon atom alkyl)- group or a halogen-pyridino-carboxamido-(2-4 carbon atom alkyl)- group or
R^{13} and R^{14}, together with an adjacent nitrogen atom to which they are attached, form a 4-(1-4 carbon atom alkyl)-piperazin-1-yl group,
where the heterocyclic groups at R^{12} and R^{14} are attached through one of their carbon atoms) and the production of pharmaceutical preparations containing such agents.

Compounds that can be used to treat brain insufficiency or improve cognitive functions are known from the literature. These compounds are predominantly 2-pyrrolidinone derivatives which are in terms of their structure very far from the cinnamic acid derivatives produced by the procedure according to the invention. These 2-pyrrolidinone derivatives are made known through such patents as Swedish patent 436 304 and European patents A-5143, 24030, 57846 and 71216.

Compounds of general formula (1) and their salts are new compounds with valuable pharmacodynamic properties. These pharmaceutical preparations can be used to treat or prevent brain insufficiency or to improve cognitive functions.

The expression alkyl group used in the description is to be understood as straight chain or branched saturated hydrocarbon groups (e.g. a methyl, ethyl, n-propyl, isopropyl, n-butyl, secondary butyl, tertiary-butyl group, etc.). The expression alkoxy group in the above relates to alkyl groups attached through an oxygen atom. The expression alkanoyl group is to be understood as groups than can be derived by removing a hydryl group from alkane-carbonic acids (e.g. acetyl group, etc.) The expression di-(alkoxycarbonyl)-alkyl group denotes alkyl groups that are substituted with an alkoxycarbonyl group on two non-adjacent carbon atoms.

R^4 is preferably a hydrogen atom. Compounds of general formula (1) are preferable in which

R^1 is a chlorine atom and R^2 and R^3 are a hydrogen atom or R^1 represents a hydrogen atom and R^2 and R^3 a chlorine atom or R^1 and R^2 represent a hydrogen atom and R^3 a fluorine atom, chlorine atom or methoxy-group. R^3 is preferably a chlorine atom and R^1, R^2 and R^4 preferably represent a hydrogen atom.

R^5 is preferably a hydrogen atom.

If R^6 is a group of general formula (a), then R^{13} preferably represents a hydrogen atom or a methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary butyl, n-nonyl, 5-nonyl, 3-pyridylmethyl or carbamoyl-methyl group. If R^6 is a group of general formula (b), then R^{13} and R^{14} preferably have the same meaning and both are hydrogen atoms or, together with the nitrogen atom to which they are attached, they represent a 4-methyl-piperazin-1-yl group or else R^{13} is a hydrogen atom and R^{14} is a 4-pyridyl, 2-phenyl-ethyl, 2-piperidinoethyl, carboxymethyl, ethoxycarbonyl-methyl, carbamoyl-methyl, 1-ethoxycarbonyl-ethyl, 1,4-bis(ethoxycarbonyl)-2-butyl or 2-(5-chloro-2-pyridinocarboxamido)-ethyl group. R^{12} preferably represents an ethyl, n-propyl, isopropyl, n-nonyl or carbamoyl-methyl group or R^{13} preferably represents a hydrogen atomand R^{14} preferably represents a hydrogen atom, an ethoxycarbonyl-methyl or 1,4-bis(ethoxycarbonyl)-2-butyl group.

R^7 appropriately represents a methyl, 3-acetyl-aminopropyl, amino or p-methoxyphenyl group – preferably a methyl or 3-acetaminopropyl group.

R^8 and R^9 are preferably identically hydrogen atoms or identically methyl groups; especially preferably they both represent a hydrogen atom.

R^{10} and R^{11} preferably form an oxo group.

Especially advantageous representatives of compounds of general formula (I) are the following derivatives:
N–[2-(4-acetamidobutyryl)-5-chloro-hydroxycinnamoyl*]-glycine ethyl ester,
[* *Hungarian 'hydroxiannamoil" should be "hydroxicinnamoil'*]
2-[4-(4-acetamido-butyramido)-butyryl] 5-chloro-hydrocinnamic acid ethyl ester,
2-[4-(4-acetamidobutyramido)-butyryl] 5-chloro-hydrocinnamic acid amide,
2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid nonyl ester,
2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid ethyl ester and
2-(4-acetamidobutyryl)-5-chloro-N–(carbamoyl-methyl)-hydrocinnamic acid amide.

The following compounds of general formula I also have advantageous characteristics:
2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid isopropyl ester,
2-[2-(4-acetamidobutyryl)-5-chloro-hydrocinnamoyl]-L-glutaminic-acid diethyl ester and
2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid carbamoyl-methyl ester.

Other advantageous representatives of compounds of general formula (1) are the following derivatives:
2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid amide and
2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid propyl ester.

According to the procedure that forms an object of our invention, compounds of general formula (I) are produced in such a way that in the case of compounds of general formula (I) containing an $-OR^{12}$ group of general formula (a) in the R^6 position, a hydrogen atom or an alkyl group of 1-10 carbon atoms in the R^{12} position, and

an oxo group in the position of R^{10} and R^{11} together, a benzazocine dione of general formula (II) (in which formula R^1, R^2, R^3, R^4, R^5, R^7, R^8 and R^9 are as given above) is treated with an acid in the presence of a compound of general formula (III) (in which formula $R^{12'}$ is a hydrogen atom or an alkyl group of 1-10 carbon atoms), then, if desired, the compound of general formula (I) obtained is subjected to one or more of the following conversions:

(i) a compound of general formula (I) containing a group of general formula (a) in the R^6 position and a hydrogen atom in the R^{12} position or a reactive derivative thereof – preferably an acid halide, an imidazolide or a silver salt – is converted by esterification into a compound of general formula (I) in which R^6 is a group of general formula (a) and R^{12} has a meaning other than a hydrogen atom,

(ii) a compound of general formula (I) containing a group of general formula (a) in the R^6 position and a hydrogen atom in the R^{12} position or a reactive derivative thereof – preferably an ester or imidazole thereof – is reacted with a compound of general formula (IV) (in which formula R^{13} is as given above and $R^{14'}$ is as given above for R^{14}, but it cannot represent a carboxy-(1-4 carbon atom alkyl)- group) or a group of general formula (b) in the R^6 position and a compound of general formula (I) containing a carboxy-(1-4 carbon atom alkyl)- group in the R^{14} position or a reactive derivative thereof is reacted with ammonia,

(iii) a compound of general formula (I) in which R^{10} and R^{11} together form an oxo group is reduced – preferably with a complex hydride, especially preferably with sodium-boron hydride or

(iv) a compound of general formula (I) containing a group of general formula (b) in the R^6 position and a (1-4 carbon atom alkoxy(-carbonyl-)-1-4 carbon atom alkyl)- group is hydrolysed into a compound of general formula (I) containing a carboxy-(alkyl group with 1-4 carbon atom alkyl)- group in the R^{14} position. [*Note: The Hungarian has an extra 'and', making the sentence meaningless.*]

During the procedure according to our invention, compounds of general formula (I) are produced in which R^6 is a group of general formula (a), R^{12} is a hydrogen atom or an alkyl group of 1-10 carbon atoms and R^{10} and R^{11} together form an oxo group.

If we desire to produce a compound of general formula (I) containing a group of general formula (a) in the R^6 position and an alkyl group of 1-10 carbon atoms in the R^{12} position from a compound of general formula (II), we use a compound of general formula (III) containing an alkyl group of 1-10 carbon atoms in the $R^{12'}$ position – that is, a suitable alcohol. The alcohol can also act as a solvent, but another solvent can also be added (e.g. a halogenated hydrocarbon such as methylene chloride). As the acid, a strong inorganic acid (e.g. concentrated hydrochloric acid) can be used as appropriate. The reaction is performed as appropriate at about room temperature; the reaction time is a period between a few hours (e.g. 10 hours) and a few days (e.g. 5 days).

If we desire to produce a compound of general formula (I) containing a group of general formula (a) in the R^6 position and a hydrogen atom in the R^{12} position, we use a compound of general formula (III) containing a hydrogen atom in the $R^{12'}$ position, that is, water. In this case, it is appropriate to proceed by dissolving the compound of general formula (II) in a polar aprotic solvent (e.g. tetrahydrofurane, acetonitrile, etc.), then an aqueous acid (e.g. dilute 2-N hydrochloric acid) is added to it. The reaction temperature and the reaction time can be as given above.

If desired, a compound of general formula (I) obtained can be subjected to one or more of the following conversions:

Esterification according to procedure (i) is performed by known methods.

The carbonic acid to be esterized is used as appropriate in the form of a reactive derivative, thus, e.g., acid halides (e.g. hydrochloric acid) or imidazolides, etc., can be used, that bring a corresponding hydroxyl compound into the reaction. During this, the carbonic acid is first converted into a reactive functional derivative (e.g. by reacting it with thionyl chloride, carbonyl di-imidazole, etc.), which in some cases is further reacted *in situ* without being isolated. Silver salts of the carbonic acid to be esterified can be also be used as the reactive functional derivative; the desired ester can be produced from the silver salts by reacting them with the appropriate halogen. The reaction conditions (e.g. temperature, reaction time, solvent, etc.) are selected depending on the characteristics of the reactive carbonic-acid derivative.

Free carbonic acids can be used, e.g. in the case of esterification with the aid of an olefin component containing a double bond. In this way, by making the free carbonic acid and isobutylene react in the presence of a small quantity of a strong inorganic acid (for example, concentrated sulphuric acid), we obtain the corresponding tertiary butyl ester.

During procedure (ii), a carbonic acid is converted into an amide substituted in some cases on the nitrogen atom, by known methods.

If a free carbonic acid is used, the reaction with a compound of general formula (IV) or ammonia can be performed in the presence of a water-splitting agent (e.g. dicyclohexyl carbodi-imide). It is appropriate to work in an inert organic solvent (e.g. in some ether, such as tetrahydrofurane*, etc.) The reaction time is several hours (e.g. 10-20 hours); the reaction temperature is appropriately room temperature.

[* *Hungarian 'tetrahidrofurában' should be 'tetrahidrofuránban'*]

As the reactive acid derivative in procedure (ii) we can use, e.g., esters, imidazolides, etc.; it is not necessary to isolate the imidazolides, but they can be further converted *in situ*. The reaction conditions (e.g. solvent, temperature, time, etc.) are selected depending on the nature of the reactive functional derivative used.

According to procedure (iii), a compound of general formula (I) can be produced in which R^{10} is a hydrogen atom and R^{11} represents a hydroxyl group. The reduction is performed appropriately with the aid of complex hydrides in an inert organic solvent. We can work in this way, e.g., with sodium-boron hydride in methanol. The reduction is performed appropriately at a temperature about room temperature; the reaction time is a period between about 1 hour and a few hours.

The hydrolysis according to procedure (iv) can be performed by known methods. We can work appropriately in an alkaline medium (e.g. with an alkali-metal hydroxide such as, e.g., sodium hydroxide) in water or a mixture of water and an organic solvent miscible with water (e.g. tetrahydrofurane). The reaction time is a period between about 1 hour and a few hours and the hydrolysis can be performed appropriately at a temperature about room temperature.

The starting materials of general formula (II) can be prepared, e.g., in such a way that a benzoquinoline derivative of general formula (V) (in which formula R^1, R^2, R^3, R^4, R^5, R^7 R^8 and R^9 are as given above) is oxidized.

Compounds of general formula (V) can be prepared in such a way that:

aa) a benzoquinolinone derivative of general formula (VI) (in which formula R^1, R^2, R^3, R^4, R^5, R^7 R^8 and R^9 are as given above) is reduced or

bb) a compound of general formula (VII) (in which formula R^1, R^2, R^3, R^4 and R^5 are as given above) is reacted in the presence of a strong base with a compound of general formula (VIII) (in which formula X is an emerging group) and the compound obtained is substituted appropriately on the nitrogen atom.

The oxidation of the benzoquinoline derivative into the corresponding benzazocine* dione of general formula (II) can be performed appropriately in an inert organic solvent (e.g. a halogenated hydrocarbon such as, e.g., chloroform, etc.) with m-chloro-perbenzoic acid, appropriately at a temperature between about -20 and about 30 °C – preferably at a temperature about -5 °C. [*_The Hungarian gives benzazecine._]

The oxidation can further be performed preferably with the aid of potassium permanganate and sodium periodate, as appropriate in a two-phase system consisting of water and an organic solvent immiscible with water (e.g. methylene chloride). To the mixture can be added preferably a phase-transfer catalyst (e.g., preferably, a quaternary ammonium salt, e.g. benzyl-triethyl ammonium chloride). The oxidation with potassium-permanganate/sodium-periodate can be performed preferably at a temperature between about 0 and 30 °C – preferably at room temperature.

The above oxidation can also be performed with other oxidizing agents or with an oxidation system (e.g. peracetic acid, hydrogen peroxide and formic acid or p-toluene-sulphonic acid, chrome-sulphuric acid, Jones reagent, etc.).

The reduction of the benzoquinoline derivative of general formula (VI) can be performed appropriately with complex hydrides (e.g. lithium-aluminium hydride, etc.) in an inert organic solvent (appropriately in some ether, e.g. tetrahydrofurane, dioxane, etc.). The reduction can be performed at a temperature between room temperature and about 120 °C. It is appropriate to work with the reaction mixture by boiling while using reflux cooling.

Compounds of general formulas (VII) and (VIII) can be reacted in the presence of a strong base (appropriately an inorganic base, such as potassium or sodium hydroxide or quaternary ammonium bases, such as benzyl-trimethyl ammonium hydroxide, etc.). The emerging group in the X position of compounds of general formula (VIII) can appropriately be a halogen atom (especially preferably a chlorine atom), but other equivalent emerging groups can also be considered (e.g. alkyl-sulphonyl oxy-groups, such as a [mezyl-oxy group] [*sic*], [arul-sulphonyl-oxy-groups] [*sic*], e.g. a benzene-sulphonyl-oxy-, p-toluene-sulphonyl-oxy- or p-bromobenzene-sulphonyl-oxy-group, etc.). The compound of general formula (VIII) is appropriately its acid-addition salt (e.g. it can be used in the form of its hydrochloride). The reaction can be performed in an inert organic solvent (e.g. an aromatic hydrocarbon such as, e.g. toluene, etc.). Compounds of general formulas (VII) and (VIII) are reacted preferably at temperatures between about 30 and about 100 °C and the reaction mixture is preferably boiled while using reflux cooling.

During both the reduction of the benzoquinolinone derivative of general formula (VI) and the reaction of compounds of general formulas (VII) and (VIII), compounds are obtained that are not substituted on the nitrogen atom and are subjected to N-acylization. For the production of compounds of general formula (II) containing an alkoxyphenyl group in the R^7 position, we use reactive derivatives of the corresponding carbonic acids (e.g. acetic-acid anhydride, carbonic-acid chlorides such as p-methoxybenzoyl chloride, etc.). For the production of compounds of general formula (II) containing an amino group at the R^7 position, the compound that is not substituted on the nitrogen atom is reacted with α-chloroacetyl isocyanate and the compound obtained is brought into a reaction with hydrazine hydrate. Compounds of general formula (II) containing an alkanoyl-amino-(alkyl group of 2-5 carbon atoms) group at the R^7 position can be produced by reacting the compound that is not substituted on the nitrogen atom with a phthalimido-(alkyl group with 2-5 carbon atoms) halide, the product obtained is converted with hydrazine hydrate to the corresponding free amine and this compound is acylized* with the corresponding reactive carbonic-acid derivative. [* Hungarian "acelezzük" should be "acilezzük"]

Compounds of general formulas (VI) and (VII) are produced appropriately in the manner shown in reaction diagram A. In the formulas, R^1, R^2, R^3, R^4, R^5, R^8 and R^9 are as given above, R^{12} and R^{13} are separately an alkyl group with a small number of carbon atoms or together with the nitrogen group to which they are attached they form a heterocyclic group (e.g. a pyrrolin-1-yl, pyrrolidin-1-yl, piperidino-, morpholino- or 4-1(alkyl group of 1-4 carbon atoms)-piperazin-1-yl group, etc.).

Compounds of general formula (VII) can be produced from compounds of general formula (IX) in one step, specifically by reacting them with ethylene or styrene, in the presence of aluminium chloride or other Lewis-acids used in reactions as a catalyst. The reaction is performed in the presence of an inert organic solvent (e.g. halogenated hydrocarbons such as methylene chloride).

Compounds of general formula (VII) can also be produced in a multi-step synthesis starting from compounds of general formula (X). The compound of general formula (X) is first reduced to a corresponding compound of general formula (XI). The reduction can be performed appropriately with complex hydrides (e.g. sodium-boron hydride, etc.). The compound obtained is dehydrated to the corresponding compound of general formula (XII), appropriately under acidic conditions (e.g. with a strong acid such as p-toluene-sulphonic acid, etc.) in a solvent immiscible with water that forms an azeootropic mixture at the reflux temperature. The water formed in the reaction is removed continuously. The compound of general formula (XII) obtained is oxidized to a compound of general formula (XIII). The oxidation can be performed appropriately with m-chloro-perbenzoic acid in an inert organic solvent (e.g. a halogenated hydrocarbon such as methylene chloride). The compound of general formula (XIII) obtained is converted to a compound of general formula (VII), by treating it with an ether solution of magnesium bromide or an organic acid (e.g. p-toluene-sulphonic acid, etc.) in an inert organic solvent (e.g. toluene, etc.),

into a compound of general formula (VII).

The compound of general formula (XIV) can be obtained by reacting a compound of general formula (VII) with an amine of general formula $HNR^{12}R^{13}$ (e.g. pyrrolidine), specifically in the presence of an acid (appropriately an organic sulphonic acid, e.g. p-toluene-sulphonic acid), in an inert organic solvent (e.g. an aromatic hydrocarbon such as benzene). The water formed in the reaction is removed from the reaction system, e.g. by adding molecular sieve or by azeotropic distillation. The compound of general formula (VI) is reacted with acrylamide, 3,3-dimethyl acrylamide or another similar compound. The acrylamide can be reacted preferably in the presence of an acid, e.g. an organic sulphonic acid (such as p-toluene-sulphonic acid) or an acidic ion exchanger, etc. at a temperature between about 100 and 200 °C – appropriately at about 100-150 °C. We can use alkanols of 1-4 carbon atoms (e.g. ethanol, etc.) as reaction media. Reaction with 3,3-dimethyl acrylamide can be performed appropriately in hydrogen* (e.g. toluene) at the boiling point of the reaction mixture.
[* *sic*]

Hydrocinnamic acid derivatives of general formula (I) and their pharmaceutically suitable salts have – as has already been mentioned – exceptionally strong pharmacodynamic properties. Their toxicity is low and, according to the following animal experiments, they protect against experimentally caused brain insufficiency.

As an experimental apparatus, we use a Skinner box provided with a grid base (30x40 cm) that can be supplied with an electric current and a platform of grey plastic (15x15x0.8 cm) in the first right corner. Untrained individuals (inexperienced male rats (100-120 g)) are placed on the platform. As soon as the animals climb down to the grid base, we administer an electric shock (0.8 mA) to their legs*. [*Hungarian uses the same word for 'leg' and 'foot' but a different word for an animal's paw.*] The normal reaction of untrained rats is to jump back to the platform. Since, however, the rats try again and again to climb down to the grid base, the electric shock has to be administered to the legs* of each animal 3-5 times. After 3-5 repeated electric shocks, the animals acquire a passive reaction – a passive avoidance response, that is, they no longer try to climb down to the grid base, because they know that they will be punished. Immediately after this, we form 3 groups of 30 animals each. The first group receives 0.3 mg/kg scopolamine in the form of an injection (i.p.) and distilled water (2 ml/kg p.o.). The second group receives 0.3 mg/kg scopolamine by injection (i.p.) and the test compound orally. The third group received only distilled water (p.o.).

After two hours, each rat is placed once on the platform in the Skinner box. In this experiment, we consider whether the animal stays on the platform for up to 60 seconds as a criterion for the effect of the test compound on staying on the platform for a short time (thus the result can only be yes or no in the case of each animal). The statistical significance of the results obtained in the first and second groups was determined by the chi-squared (χ^2) test.

2-5 hours after acquiring the passive avoidance response, only 70-75% of the animals were given distilled water (per oram) only, so they had to stay on the platform. In the animals given scopolamine (0.3 mg/kg, i.p.) and distilled water (p.o.), we observed a retrograde effect lasting 3-4 hours in 85-92%, that is, the animals forgot that they had to stay on the platform. The blocking of the short-term memory caused by injection of 0.3 mg/kg scopolamine can be protected against by compounds that act against brain insufficiency. The dosage of the test compound, however, is regarded as active against scopolamine if the number of positive (yes) results differs significantly from the corresponding values observed in the animals treated with scopolamine (0.3 mg/kg, i.p.) and the control animals that received distilled water (p.o.) only. In Table I, we report whether certain compounds of general formula (I) have a significant effect during the above test and at which dosage. The acute toxicity value (DL_{50}, mg/kg, in mice, with a single oral dose) is also shown in the table.

Table I

R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	$R^{10}R^{11}$	Significantly effective dosage, mg/kg, p.o.	DL_{50}, mg/kg, p.o.
H	H	Cl	H	H	$-NHCH_2COOC_2H_5$	$-CH_3$	H	H	oxo	0.003 0.03 0.3 3 10	> 5000
H	H	Cl	H	H	$-OC_2H_5$	$-(CH_2)_3NHCOCH_3$	H	H	oxo	0.003 0.03 0.3	> 5000
H	H	Cl	H	H	$-NH_2$	$-(CH_2)_3NHCOCH_3$	H	H	oxo	0.00001 0.00003 0.0003 0.003 0.03	
H	H	Cl	H	H	$OCH(CH_3)_2$	$-CH_3$	H	H	oxo	0.01 0.03 0.1 0.3 1 3 10 30	> 4000
H	H	Cl	H	H	$-OC_2H_5$	$-CH_3$	H	H	oxo	0.03 0.1 0.3 3	> 5000
H	H	Cl	H	H	$-NH-CH(-(CH_2)-COOC_2H_5)-COOC_2H_5$	CH_3	H	H	oxo	0.1 0.3 3	> 5000
H	H	Cl	H	H	$-OCH_2CONH_2$	CH_3	H	H	oxo	0.03 0.3 1	

Table I

R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	$R^{10}R^{11}$	Significantly effective dosage, a	DL_{50}, mg/kg, p.o.
H	H	Cl	H	H	$-NH_2$	$-CH_3$	H	H	oxo	0.03 0.3	> 4000
H	H	Cl	H	H	$-O-(CH_2)_2-CH_3$	$-CH_3$	H	H	oxo	0.1 0.3	> 5000
H	H	Cl	H	H	$-O-(CH_2)_8-CH_3$	$-CH_3$	H	H	oxo	0.03 0.1 0.3 3	> 5000

Compounds of general formula (I) can be used in pharmaceuticals. They can be formed into preparations that can be administered orally (e.g. tablets, coated tablets, lozenges, hard and soft gel capsules, solutions, emulsions, or suspensions), rectally (e.g. suppositories) or parenterally (e.g. injection solution).

Another object of our invention is a procedure for producing pharmaceutical preparations in such a way that a compound of general formula (I) and, if desired, one or more additional medicinal agents, is mixed with inert excipients and brought into a galenic form.

Tablets, coated tablets, lozenges, and hard gel capsules can contain as excipients, e.g., lactose, maize starch or derivatives thereof, talc, stearic acid or salts thereof, etc.

In the preparation of soft gel capsules, plant oils, waxes, fats, semisolid or liquid polyols, etc., for example, can be used.

In the preparation of solutions and syrups, excipients that can be used include, e.g., water, polyols, saccharose, invert sugar, glucose, etc.

Solutions for injection can contain, e.g., water, alcohols, polyols, glycerine, plant oils, etc. as excipients.

In the preparation of suppositories, natural or hardened oils, waxes, fats, semisolid or liquid polyols, etc., for example, can be used.

Pharmaceutical preparations can also contain preservatives, solvents, sweeteners, colorants and flavourings, moisteners, stabilizers, emulsifiers, salts that cause changes in osmotic pressure, buffers, coating materials or antioxidants, as well as other pharmaceutically significant substances in some cases.

Compounds of general formula (I) can be used to treat or prevent brain insufficiency or to improve cognitive functions (e.g., memory ability, learning ability, interest in one's surroundings, and taking care of oneself), e.g., in geriatrics, poisonings (e.g. alcoholism), and in the case of disturbances to brain circulation. Other fields of use are vestibular disorders (e.g., Menière's disease) and developmental disorders (e.g. dyslexia). The dosage of compounds of general formula (I) can vary within wide limits and will always depend on the circumstances and requirements of the particular situation. The daily dosage of compounds of general formula (I) is generally between 1 and 2500 mg approximately, but this is only an illustrative value, and the upper limit can also be exceeded if necessary.

Further details of our procedure are presented in the following examples, without our invention being limited to the examples.

Example 1

a) 1155 g (6.4 mmol) 6-chloro-3,4-dihydro-2(1H)-naphthalene is dissolved in 5 litres toluene, then 500 g (7.0 mmol) pyrrolidine and after that a solution of 26 g (0.14 mol) p-toluene-sulphonic-acid monohydrate in toluene is added to it in drops. The reaction mixture is boiled on a water separator, using reflux cooling. After some 120 ml water has been thus separated, 4 litres toluene is distilled down and the reaction mixture is allowed to cool slowly. A solid material crystallizes out, which is filtered and

washed with acetone. The 1-(6-chloro-3,4-dihydro-2-naphthyl) pyrrolidine obtained melts at 117-118 °C. The yield is 1087 g (73%). After evaporation, suspending the residue in ether, filtering it and washing with acetone, another 217 g of the above product is obtained. The melting point is 117-118 °C and total yield is 87%.

b) 70 g Amberlite IR200 is added to a mixture of 701 g (3 mol) 1-6(chloro-3,4-dihydro-2-naphthyl) pyrrolidine, 640 g (19 mmol) acrylamide and 7 litres ethanol. The reaction mixture is boiled for 3 days, using reflux cooling, then the solid material that precipitates out is filtered and crystallized by dioxane extraction. The 8-chloro-1,4,5,6-tetrahydrobenze[f]quinoline-3(2H)-one obtained melts at 228-230 °C. Yield: 505 g (72%).

c) 147 g (1.94 mmol) lithium-aluminium hydride is suspended in 4 litres tetrahydrofurane in an argon atmosphere, then 454 g (1.94 mol) 8-chloro-1,4,5,6-tetrahydrobenzo[f]quinolin-3(2H)-one is added to it. The reaction mixture is boiled for 2.5 hours, using reflux cooling, then cooled down, 470 ml 18% sodium hydroxide solution is added to it in drops, it is stirred for 30 minutes at room temperature, filtered, and the residue remaining in the filter is washed with tetrahydrofurane. After the filtrate has been evaporated, we obtain 8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline as a yellow oil. Yield: 424 g (99%).

d) 229 g (1.04 mol) 8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline is dissolved in 2 litres methylene chloride, then it is mixed with 115 g (1.1.4) triethyl amine and 89.5 g (1.14 mol) acetyl chloride and 400 ml methylene chloride are added to it in drops at 0 °C. The reaction mixture is stirred at room temperature for one hour, then poured into water, extracted with methylene chloride, the methylene-chloride phase is dried over sodium sulphate and the solvent is removed under vacuum. The product is suspended in 500 ml ether and filtered. The 4-acetyl-8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinolin obtained melts at 106-108 °C. After evaporation and chromatography (silicic-acid gel chloroform) a further portion of the product with a melting point of 106-108 °C is obtained Yield: 154 g (56%).

4-acetyl-8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline can also be prepared in the following way:

100 g (0.55 mol) 6-chloro-3,4-dihydro-2(1H)-naphthalinone is dissolved in 2 litres toluene, 64.0 g ground potassium hydroxide is added to it, the mixture is boiled, using reflux cooling, then 165 g 3-(chloropropyl) amine hydrochloride is added to it in portions over a period of 10 minutes. The reaction mixture is heated under a water separator until no more reactant can be detected by thin-layer chromatography. The reaction mixture is cooled to room temperature, then it is mixed with 155 ml triethyl amine. A solution formed from 60 ml acetyl chloride in 450 ml toluene is added to the mixture in drops with ice cooling – the internal temperature must not rise above 25 °C. The reaction mixture is stirred at room temperature for one hour, then extracted with a mixture of water and methylene chloride and dried over magnesium sulphate, and the solvent is extracted under vacuum. 140 g (96%) 4-acetyl-8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline is obtained in the form of brown crystals. The raw product can be used in the following reaction step:

e) 115 g (0.44 mol) 4-acetyl-8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline is dissolved in 1 litre methylene chloride and a suspension made from 189 g (0.93 mol) m-chloro-perbenzoic acid (85%) and 500 ml methylene chloride is added to it in drops at 0°C. The reaction mixture is mixed for one hour at room temperature, then the precipitate that separates out is filtered and extracted with a solution of 2-N sodium hydroxide and water. The organic phase is extracted with a magnesium hydroxide solution and water. The organic phase is distilled down and the residue is re-crystallized with an ethyl acetate ether mixture. The 4-acetyl-11-chloro-1,2,4,5,6,7-hexahydro-4-benzazocine-2,8-dione obtained forms white crystals that melt at 154-156 °C. Yield: 89.5 g (69%).

f) 1 ml concentrated hydrochloric acid is added to a solution of 4.00 g (0.014 mol) 4-acetyl-11-chloro-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione and 200 ml methanol, and the reaction mixture is stirred for 20 hours at room temperature. The solution is evaporated, the residue is extracted with a mixture of methylene chloride and water and dried over magnesium sulphate, and the solvent is removed in vacuum. After chromatography with silicic-acid gel and elution with ethyl acetate, followed by chromatography with aluminium oxide and elution with ethyl acetate, and finally crystallization with tertiary butyl-methyl ether, 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid methyl ester is obtained, with a melting point of 46-48 °C. Yield: 2.17 g (50%).

Example 2

5 ml concentrated hydrochloric acid is added to a solution made with 4.00 g (0.014 mol) 4-acetyl-11-chloro-1,2,4,5,6,7-hexahydro-3-benzazocine 3,8-dione and 250 ml ethanol, and the reaction mixture is stirred for 30 hours at room temperature. The solution is evaporated, the residue is extracted with a mixture of methylene chloride and water and dried above magnesium sulphate, and the solvent is removed in vacuum. The residue is cromatographed with silicic-acid gel and eluted with a 2:1 mixture of ethyl acetate and hexane and crystallized from ether. 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid ethyl ester is obtained in the form of drab-coloured crystals with a melting point of 64-66 °C. Yield: 2.20 g (48%).

Example 3

10 ml concentrated hydrochloric acid is added to a solution of 7.35 g (0.025 mol) 4-acetyl-11-chloro-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione and 400 ml n-propanol, and the reaction mixture is stirred for 24 hours at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and evaporated under vacuum. The residue is chromatographed with silicic-acid gel and eluted with a 2:1 mixture of ethyl acetate and hexane, and crystallized from the ethyl acetate/hexane mixture. 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid isopropyl ester is obtained in the form of white crystals with a melting point of 35-37 °C. Yield: 6.70 g (76%).

Example 4

5 ml concentrated hydrochloric acid is added to a solution of 4.00 g (0.014 mol) 4-acetyl-11-chloro-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione and 250 ml isopropanol, and the reaction mixture is stirred at room temperature for 24 hours. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is removed in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 2:1 mixture of ethyl acetate and hexane, and crystallized from ether. We obtain 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid isopropyl ester in the form of white crystals with a melting point of 35-37 °C. Yield: 2.30 g (48%).

Example 5

15 ml concentrated hydrochloric acid is added to a solution of 10.00 g (0.034 mol) 4-acetyl-11-chloro-1,2,4,5,6,7-hexahydro-3-benzazocine 3,8-dione, 70 ml butanol and 50 ml methylene chloride, and the reaction mixture is stirred for 18 hours at room temperature. The solution is evaporated, extracted with methylene chloride and water [*sic*] and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel, eluted with ethyl acetate, then crystallized from ether. We obtain 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid butyl ester in the form of white crystals with a melting point of 56-57 °C. Yield: 5.40 g (43%).

Example 6

15 ml concentrated hydrochloric acid is added to a solution of 10.00 g (0.034 mol) 4-acetyl-11-chloro-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione, 90 ml n-nonanol and 50 ml methylene chloride, and the reaction mixture is stirred for 15 hours at room temperature. The solution is evaporated and the residue extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid get, eluted with a 4:1 mixture of ethyl acetate and hexane and crystallized from ether. We obtain 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid nonyl ester in the form of white crystals with a melting point of 55-57 °C. Yield: 6.10 g (41%).

Example 7

15 ml concentrated hydrochloric acid is added to a solution of 10.00 g (0.034 mol) 4-acetyl-11-chloro-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione, 90 ml 5-nonanol [sic] and 50 ml methylene chloride, and the reaction mixture is stirred for 18 hours at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel and eluted with ethyl acetate. We obtain 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid 1-butyl-pentyl ester in the form of a yellow oil.
Yield: 370 g (25%). IR spectrum (film): 3297 m, 2956 s, 2933 s, 2862 s, 1728 s, 1686 s, 1654 s, 1591 s, 1558 s, 1448 s, 1367 s, 1290 s, 1235 s, 1186 s.

Example 8

a) A solution of 31.4 g (0.143 mmol) 8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline and 300 ml methylene chloride is added to a solution of 36.0 g (0.143 mol) 4-phthalimidobutyric-acid chloride and 360 ml methylene chloride at 0 °C, then the reaction mixture is stirred for one hour at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and an aqueous solution of sodium bicarbonate, and dried over magnesium sulphate, and the solvent is distilled down in vacuum. After extraction crystallization from acetone, 8-chloro-1,2,3,4,5,6-hexahydro-4-(4-phthalimidobutyryl) benzo[f]quinoline is obtained in the form of crystals with a melting point of 182-183 °C. Yield: 39.6 g (64%).

b) A suspension of 10.9 g (0.025 mol) 8-chloro-1,2,3,4,5, 6-hexahydro-4-(4-phthalimidobutyryl benzo[f]quinoline and 3.2 ml (0.065 mol) hydrazine hydrate is boiled for 2 hours, using reflux cooling. The solution is evaporated, the residue is extracted with methylene chloride and water, and dried over sodium sulphate, and the solvent is removed in vacuum. The residue is dissolved in 10 ml 5.5-N methanol in hydrochloric acid, and the product is precipitated with ether. After re-crystallization from a mixture of methanol and ether, 4-(4-aminobutyryl) 8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline hydrochloride is obtained in the form of drab crystals with a melting point of 225 °C. Yield: 4.55 g (60%).

c) 5 ml (0.306 mol) triethyl amine is added to a suspension of 5.09 g (0.015 mol) 4-(4-aminobutyryl) 8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline and 50 ml methylene chloride, then a solution made from 1.33 ml (0.019 mol) acetyl chloride in 15 ml methylene chloride is added at 0 °C. The reaction mixture is stirred at room temperature for one hour, then extracted with a mixture of methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is crystallized from a mixture of methylene chloride and ether, chromatographed on silicic-acid gel, eluted with a 9:1 mixture of ethyl acetate and methanol and finally crystallized again from a mixture of methylene chloride and ether. We obtain 4.16 g (80%) N–[4-(8-chloro-2,3,5,6-tetrahydrobenzo[f]quinolin-4(1H)-yl)-oxo-butyl acetamide in the form of white crystals with a melting point of 142-143 °C.

d) A solution made from 4.80 g (0.024 mol) 85% m-chloro-perbenzoic acid and 50 ml methylene chloride is added to a solution of 4.00 g (0.016 mol) N–4-(8-chloro-2,3,5,6-tetrahydrobenzo[f]quinolin-4-(1H)-yl)-4-oxobutyl acetamide and 40 ml methylene chloride at 0 °C. The reaction mixture is stirred at room temperature for one hour, then extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is removed in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 9:1 mixture of ethyl acetate and methanol and crystallized from a mixture of ethyl acetate and hexane. We obtain N–[3-{(11-chloro-2,3,5,6,7,8-hexahydro-3,8-dioxo-4-benzazocine-4(1H)-yl)-carbonyl]-propyl} acetamide in the form of white crystals with a melting point of 135-136 °C.

e) 1 ml concentrated hydrochloric acid is added to a solution of 2.66 g (0.007 mol) N–[3-[(11-chloro-2,3,5,6,7,8-hexahydro-3,8-dioxo-4-benzazocin-4(1H)-yl)-carbonyl]-propyl] acetamide, 100 ml ethanol and 30 ml methylene chloride, and the reaction mixture is stirred for 5 days at room temperature. The solution is evaporated and the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on aluminium oxide, eluted with a 19:1 mixture of ethyl acetate and ethanol, and crystallized from a mixture of methylene chloride and ether. We obtain 2-[4-(4-acetamido-butyramido)-butyryl] 5-chloro-hydrocinnamic acid ethyl ester in the form of white crystals with a melting point of 95 °C. Yield: 1.90 g (64%).

Example 9

a) 15.0 g (0.06 mol) 8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline is dissolved in 150 ml methylene chloride, then a solution of 11.2 g (0.066) mol p-methoxybenzoyl chloride in 50 ml methylene chloride is added at 0 °C in drops. The reaction mixture is stirred for one hour at room temperature, then extracted with water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. After crystallization from a mixture of methylene chloride and ether, we obtain 4-(p-methoxybenzoyl) 8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline in the form of white crystals with a melting point of 182-183 °C.

Yield: 8.80 g (42%).

b) 8.80 g (0.025 mol) 4-(p-methoxybenzoyl)-8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline is dissolved in 100 ml chloroform and 10.3 g (0.051 mol) of a suspension made from 85% m-chloro-perbenzoic acid in 100 ml chloroform is added to it at 0 °C in drops. The reaction mixture is stirred for one hour at room temperature, then extracted with 2-N sodium-hydroxide solution and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 2:1 mixture of ether and hexane, and crystallized from a mixture of ether and hexane. We obtain 4-(p-methoxybenzoyl)-11-chloro-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione in the form of white crystals with a melting point of 143 °C. Yield: 5.13 g (53%).

c) 5 ml concentrated hydrochloric acid is added to a solution of 3.60 g (0.009 mol) 4-(p-methoxybenzoyl)-11-chloro-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione, 200 ml methanol, and 50 ml methylene chloride, and the reaction mixture is stirred for 60 hours at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium* sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 1:1 mixture of hexane and ethyl acetate, and crystallized from a mixture of methylene chloride and hexane. We obtain 2-[4-(p-methoxybenzoyl)-amidobutyryl]-5-chloro-hydrocinnamic acid methyl ester in the form of white crystals with a melting point of 111 °C. [* *Hungarian 'mangézium' should be 'magnezium'.*]

Example 10

500 ml 2-N hydrochloric acid is added to a solution made from 103 g (0.35 mol) 4-acetyl-11-chloro-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione in 1 litre tetrahydrofurane. The reaction mixture is stirred over one night at room temperature, then evaporated in vacuum, and the residue is mixed with methylene chloride and extracted twice with a 2-N sodium-hydroxide solution. The aqueous phase is acidified with 6-N hydrochloric acid and extracted with methylene chloride . The solvent is distilled down in vacuum and the residue is chromatographed on silicic-acid gel and eluted with a 20:1 mixture of methylene chloride and methanol. The 2-(4-acetamidobutyryl) 5-chloro-hydrocinnamic acid obtained has a melting point of 90-92 °C. Yield: 72.8 g (67%).

Example 11.

a) A solution of 154.8 g 2-chlorophenyl-acetyl chloride in 290 ml methylene chloride is added in drops while stirring to a mixture of 218 g aluminium chloride and 1000 ml methylene chloride. Ethylene is fed into the mixture for 40 minutes at 0-5 °C , then it is stirred for one hour and mixed with 570 ml water at 0-5 °C. The methylene-chloride phase is washed twice with a solution of 500 ml 2-N hydrochloric acid, twice with 500 ml sodium-bicarbonate solution, and 700 ml water, dried over sodium sulphate, and washed with 700 ml water, and evaporated in vacuum. The product, 8-chloro-3,4-dihydro-2(1H)-naphthalenone, which melts at 56-59 °C, is obtained by crystallization from a petroleum ether with a low boiling point. Yield: 117 g (65%).

b) 70.0 g 8-chloro-3,4-dihydro-2(1H)-naphthalenone in 550 ml benzene and 33 ml pyrrolidine is boiled in the presence of 1.4 g toluene-sulphonic acid for 2.5 hours, using reflux cooling. The raw 1-(8-chloro-3,4-dihydro-2-naphthyl) pyrrolidine can be converted further without additional purification. Yield: 89.4 (99%).

c) 56.0 acrylamide and 3.0 anhydrous p-toluene sulphonic acid are added to 89.4 g raw 1-(8-chloro-3,4-dihydro-2 naphthyl) pyrrolidine, the reaction mixture is warmed in a nitrogen atmosphere at 100 °C and 150 °C for 2 hours each, then extracted with methylene chloride, and the solvent is distilled down in vacuum. After re-crystallization from ethyl acetate, the 10-chloro-1,4,5,6-tetrahydrobenzo[f]quinoline-3(2H)-one melts at 186-187 °C. Yield: 31.7 g (35%).

d) 2.0 g 10-chloro-1,4,5,6-tetrahydrobenzo[f]quinolin-3(2H)one is added to a suspension of 6.49 g lithium-aluminium hydride and 240 ml anhydrous tetrahydrofurane in a nitrogen atmosphere, with stirring, over 35 minutes, at 20-25 °C, in parts. The reaction mixture is boiled for 150 minutes using reflux cooling, then cooled, mixed with 2.0 ml 6.4-N sodium-hydroxide solution at 0-10 °C, filtered, and washed several times with 20 ml tetrahydrofurane each time. The solvent is distilled down in vacuum. The 10-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline obtained is converted further immediately.

e) 20.1 g raw 10-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline is dissolved in 40 ml pyridine and 36 ml acetic-acid anhydride, the solution is allowed to stand at room temperature of 20 hours, then evaporated, the residue is taken up twice into 150 ml toluene each time, and the solution obtained is evaporated. The residue is chromatographed on silicic-acid gel and eluted with chloroform. The 11.2 g (50%) 4-acetyl-10-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline obtained by re-crystallization from isopropyl ether melts at 117-118 °C.

f) 16.0 g of a solution formed from 85% m-chloro-perbenzoic acid in 205 ml chloroform is added to 8.50 g 4-acetyl-10-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline and 205 ml chloroform. The reaction mixture is stirred for 4 hours at room temperature, then 4 g potassium iodide and 70 ml water and sodium thiosulphate are added to it until it is colourless. The chloroform phase is washed with 2-N sodium hydroxide solution and twice with water and evaporated in vacuum. The residue is chromatographed on 100 g silicic-acid gel and eluted with methylene chloride. The 4-acetyl-9-chloro-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione obtained after re-crystallization from isopropyl ether melts at 115-116 °C. Yield: 7.34 g (74%).

g) 1 ml 25% hydrochloric acid is added to solution of 5.00 g (0.017) 4-acetyl-9-chloro-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione and 153 ml methanol, and the reaction mixture is stirred for 4 days at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and an aqueous solution of sodium bicarbonate, dried over sodium sulphate, and the solvent is removed in vacuum. The residue is chromatographed on silicic-acid gel and eluted, first with methylene chloride, then with ethyl acetate, and finally re-crystallized from petroleum ether*. We obtain 2-(4-acetamidobutyryl)-3-chloro-hydrocinnammic-acid methyl ester in the form of white crystals with a melting point of 51-52 °C. Yield: 4.07 g (73%).
[* *Hungarian 'pteroléterbôl' should be 'petroléterbôl'*]

Example 12

a) A solution made from 149.4 g 4-fluorophenyl-acetic-acid chloride in 300 ml methylene chloride is added in drops to a solution of 230 g aluminium chloride and 1050 ml methylene-chloride at 0-5 °C, while stirring, over 60 minutes. Ethylene is fed into the mixture for 30 minutes at 0-5 °C, then it is stirred for an hour at room temperature and mixed for half an hour at 0-5 °C with 600 ml ice water. The

methylene-chloride phase is washed with 2-N hydrochloric acid, water, and saturated bicarbonate, dried over sodium sulphate, and the residue is distilled down in vacuum. The residue is mixed with 250 ml petroleum ether with a low boiling point, left to stand for one night in a refrigerator and then filtered. The 6-fluoro-3,4-dihydro-2(1H)-naphthalenone obtained melts at 50-60 °C. Yield: 128 g (82%).

b) A mixture of 16.7 g 6-fluoro-3,4-dihydro-2(1H)-naphthalenone, 200 ml benzene, 8.4 ml pyrrolidine and 0.35 g anhydrous p-toluene sulphonic acid. is boiled for 2.5 hours, using reflux cooling. The 1-(6-fluoro-3,4-dihydro-2-naphthyl) pyrrolidine obtained is mixed with 10.8 g acryl amide and 0.5 g p-toluene sulphonic acid, without further purification. The reaction mixture is heated under nitrogen at 100 °C and 150 °C for 2 hours each, then dissolved in 180 ml chloroform, washed with water, chromatographed on 150 g silicic-acid gel and eluted with chloroform. After re-crystallization from ethyl acetate, we obtain 8-fluoro-1,4,5,6-tetrahydrobenzo[f]quinoline 3(2H)-one with a melting point of 223-224 °C. Melting point: 223-224 °C. Yield: 11.7 g (53%).

c) 6.20 g 8-fluoro-1,4,5,6-tetrahydrobenzo[f]quinolin-3(2H)one is added to 2.17 lithium-aluminium hydride and 60 ml anhydrous-tetrahydrofurane suspension over 35 minutes in parts at 20-25 °C. The reaction mixture is boiled for 150 minutes, using reflux cooling, then mixed with 7.0 ml 6.5-N sodium-hydroxide solution at 0-10 °C. The mixture is filtered, washed several times with 20 ml tetrahydrofurane each time, then the solvent is distilled down in vacuum. The 8-fluoro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline obtained is converted further immediately.

d) A solution of 6.00 g raw 8-fluoro-1,2,3,4,5,6-hexahydrobenzo[f[quinoline, 13 ml pyridine and 12 ml acetic-acid anhydride is allowed to stand for 20 hours at room temperature, and the reaction mixture is then evaporated. The residue is taken up into toluene twice, and the solution obtained is evaporated until dry. The residue is chromatographed on 150 g silicic-acid gel and eluted with methylene chloride. The 4-acetyl-8-fluoro-1,2,3,4,5,6-hexahydro-4-benzazocine 3,8-dione obtained after re-crystallization from isopropyl ether melts at 101-102 °C. Yield: 4.9 g (70%).

e) A solution formed from 2.48 g (4-acetyl-8-fluoro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline and 60 ml chloroform is mixed with a solution of 5.24 g 85% m-chloro-perbenzoic acid and 40 ml chloroform and the reaction mixture is stirred for 3 hours at room temperature. After his, a solution of 1.10 g potassium iodide and 15 ml water is added to it, then sodium thiosulphate is added until the discolouration disappears. The chloroform phase is separated away, washed with 15 ml 2-N sodium-hydroxide solution and twice with 40 ml water, the chloroform is distilled down in vacuum, and the residue is re-crystallized from ethyl acetate. The 4-acetyl-11-fluoro-1,2,4,5,6,7-hexachloro-4-benzazocine 3,8-dione obtained melts at 161-16* °C. Yield: 2.16 g (77%).

[* one digit missing]

f) 20 ml 2-N hydrochloric acid is added to a solution of 3.00 g (0.011 mol) 4-acetyl-11-fluoro-1,2,3,4,5,6,7-hexahydro-4-benzazocine 3,8-dione and 40 ml acetonitrile and the reaction mixture is stirred at room temperature for 65 hours. The solvent is evaporated, the residue is chromatographed on silicic-acid gel, eluted with tetrahydrofurane, and re-crystallized from ether. We obtain 1.80 g (57%) 2-(4-acetamido-butyryl) 5-fluoro-hydrocinnamic acid in the form of which crystals with a melting point of 100-101 °C.

Example 13

0.75 ml 25% hydrochloric acid is added to a solution of 5.00 g (0.018 mol) 4-acetyl ll-fluoro-1,2,4,5,6,7-hexahydro-4-benzazecine 3,8-dione and 163 ml methanol. The reaction mixture is stirred at room temperature for 99 hours, then the solution is evaporated. The residue is extracted with toluene and saturated sodium-bicarbonate solution and dried over sodium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a mixture of chloroform and ethyl acetate, then chromatographed on aluminium oxide and eluted with methylene chloride and ethyl acetate, and finally mixed with petroleum ether. 2-(4-acetamidobutyryl) 5-fluoro-hydrocinnamic acid methyl ester is obtained in the form of slightly yellow crystals with a melting point of 39-40 °C. Yield: 4.46 g (80%).

Example 14

a) A solution made from 12.0 g 6-methoxy-2-tetralone and 200 ml benzene is boiled for 2 hours, using reflux cooling, in the presence of 0.5 g anhydrous p-toluene-sulphonic acid. The toluene is removed in vacuum. 9.70 g acrylamide and 0.5 g p-toluene-sulphonic acid are added to the raw 1-(6-methoxy-3,4-dihydro-2-naphthyl) pyrrolidine. The reaction mixture is heated in a nitrogen atmosphere at 100 °C and 150 °C for 2 hours each, then extracted with chloroform and water and dried over sodium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on 160 g silicic-acid gel, eluted with methylene chloride, and re-crystallized from ethyl acetate. The 8-methoxy-1,4,5,8-tetrahydrobenzo[f]quinolin-3(2H)-one obtained has a meltingpoint of 208-209 °C. Yield: 9.4 g (60%).

b) 5.10 g 8-methoxy-1,4,5,8-tetrahydrobenzo[f]quinolin-3(2H)-one is added to a suspension of 1.69 g lithium-aluminium hydride and 50 ml anhydrous tetrahydrofurane in portions in a nitrogen atmosphere at 20 °C, while stirring. The reaction mixture is boiled for 150 minutes, using reflux cooling, then mixed with 6.5-N sodium-hydroxide solution at 0-10 °C. The reaction mixture is filtered and washed with tetrahydrofurane, and the solvent is distilled down in vacuum. The 8-methoxy-1,2,3,4,5,6-hexahydrobenzo[f]quinoline is converted further immediately. Yield: 4.7 g (raw product).

c) A mixture of 4.70 g 8-methoxy-1,2,3,4,5,6-hexahydrobenzo[f]quinoline, 15 ml pyridine, and 11 ml acetic-acid anhydride is allowed to stand for 20 hours at room temperature, then the reaction mixture is evaporated and the residue is taken up twice into 50 ml anhydrous toluene each time, and the solutions obtained are evaporated until dry. The residue is chromatographed on 50 g silicic-acid gel and eluted with methylene chloride. The 4-acetyl-8-methoxy-1,2,3,4,5,6-hexahydrobenzo[f]quinoline obtained melts at 119-120 °C (after re-crystallization from isopropanol and ether). Yield: 2.0 g (50%).

d) A solution of 38.0 g 85% m-chloro-perbenzoic acid and 250 ml chloroform is added in drops to a solution of 21.3 g 4-acetyl-8-methoxy-1,2,3,4,5,6-hexahydrobenzo[f]quinoline and 200 ml chloroform at 0-5 °C. The reaction mixture is stirred for 18 hours at room temperature and mixed with sodium iodide and water, then sodium thiosulphate is added to it until it becomes colourless. The chloroform phase is washed with ammonium-hydroxide solution and sodium-chloride solution and dried over sodium sulphate, and

evaporated in vacuum. The 4-acetyl-11-methoxy-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione obtained after re-crystallization from ethyl acetate has a melting point of 156-158 °C. Yield: 12.9 g (54%).

e) 5 ml concentrated hydrochloric acid is added to a solution of 5.50 g (0.019 mol) 4-acetyl-11-methoxy-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione and 150 ml ethanol, and the reaction mixture is stirred over one night at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is removed in vacuum. The residue is chromatographed on silicic-acid gel and eluted with ethyl acetate and finally re-crystallized from a mixture of ethyl acetate and ether. We obtain 2-(acetamidobutyryl) 5-methoxycinnamic acid ethyl ester in the form of white crystals that melt at 59-61 °C. Yield: 4.25 g (67%).

Example 15

a) 9.00 g (0.042 mol) 6,7-dichloro-3,4-dihydro-2(1H)-naphthalone and 0.3 g p-toluene-sulphonic acid is dissolved in 200 ml pyridine, then 3.5 ml (0.042 mol) pyrrolidine is added to it in drops and the reaction mixture is boiled for 2 hours, using reflux cooling. The solvent is distilled down in vacuum, 200 ml ether is added to the residue, and the crystals that form are filtered. The 1-(6,7-dichloro)-3,4-dihydro-2-naphthyl) pyrrolidine obtained has a melting point of 141-142 °C. Yield 90%.

b) A melt of 10.1 g (0.038 mol) 1-(6,7-dichloro-3,4-dihydro-2-naphthyl) pyrrolidine, 5.36 g (0.075 mol) acrylamide and 0.3 g p-toluene-sulphonic acid is stirred in a nitrogen atmosphere for 2 hours at 100 °C, then for 2 hours at 150 °C. The cake is re-crystallized from ethanol. The 8,9-dichloro-1,4,5,6-tetrahydrobenzo[f]quinolin-3(2H)-one obtained melts at 260-261 °C. Yield: 55%.

c) 1.57 g (0.042 mol) lithium-aluminium hydride is suspended in 60 ml tetrahydrofurane in an argon atmosphere, then 5.6 g (0.021 mol) 8,9-dichloro-1,4,5,6-tetrahydrobenzo[f]quinolin-3(2H)-one is added to it and the reaction mixture is boiled for 2.5 hours, using reflux cooling. The reaction mixture is cooled to 0 °C, 5.2 ml 18% sodium-hydroxide solution is added to it, and the precipitate that separates out is filtered. After the filtrate is evaporated, 8,9-dichloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline * is obtained in the form of a yellow oil, which is converted further immediately. [* *Hungarian 'xinolint' = 'kinolint'.*]

d) 6.17 g (0.024 mol) 8,9-dichloro-1,2,3,4,5,6 hexahydrobenzo[f]quinolin * is dissolved in 10 ml pyridine, then 9 ml (0.09 mol) acetic-acid anhydride is added to it in drops and the reaction mixture is stirred for 17 hours at room temperature. After this, it is chromatographed on silicic-acid gel and eluted with chloroform. The resultant product is suspended in ether and filtered. The 4-acetyl-8,9-dichloro-1,2,3,4,5,6-hexahydro-benzo[f]quinoline obtained has a melting point of 146-148 °C. Yield: 67%.

[* *Hungarian 'tetrahdiro' should be 'tetrahidro'.*]

e) 4.14 g (0.014 mol) 4-acetyl-8,9-dichloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline is dissolved in 70 ml chloroform and a suspension of 7.28 g (0.036 mol) m-chloro-perbenzoic acid (85%) in 100 ml chloroform is added to it in drops. The reaction mixture is stirred for 3 hours, then the precipitate that separates out is filtered and extracted with a solution of potassium iodide and sodium thiosulphate. After this, it is chromatographed on silicic-acid gel, eluted with chloroform, and re-crystallized from isopropyl ether. 4-acetyl-10,11-dichloro-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione is obtained in the form of white crystals with a melting point of 163-165 °C.

f) 2 ml concentrated hydrochloric acid is added to a solution of 1.75 g (0.005 mol) 4-acetyl-10,11-dichloro-1,2,4,5,6,7-hexahydro-4-benzazocine-3,8-dione in 60 ml ethanol, and the reaction mixture is stirred for 20 hours at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium* sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel, eluted with methylene chloride, and finally crystallized from tertiary butyl-methyl ether. We obtain 0.45 g (23%) 2-(4-acetamidobutyryl)-4,5-dichloro-hydrocinnamic-acid ethyl ether in the form of white crystals with a melting point of 63-65 °C.

[* *Hungarian 'mangézium' should be 'magnézium'*]

Example 16

a) A suspension of 127 g (0.7 mol) 6-chloro-2-tetralone, 70.0g (0.7 mol) 3,3-dimethyl acrylamide, 63.6 ml (0.042 mol) tetramethoxysilane and 85.3 g (0.56 mol) caesium fluoride in 400 ml toluene is boiled for 18 hours, using reflux cooling, then the solvent is evaporated in vacuum. After extraction with methylene chloride and water, it is chromatographed on silicic-acid get, eluted with a 1:1 mixture of ethyl acetate and hexane, and re-crystallized from a mixture of methylene chloride and hexane. We obtain 8-chloro-1,1-dimethyl 1,2,5,6-tetrahydrobenzo[f]quinoline 3-one in the form of white crystals with a melting point of 213 °C. Yield: 12.2 g (7%).

b) 3.36 g (0.089 mol) lithium-aluminium hydride is suspended in 100 ml tetrahydrofurane in an argon atmosphere, then 11.6 g (0.044 mol) 8-chloro-1,1-dimethyl 1,2,5,6-tetrahydrobenzo[f]quinoline 3-one is added to it slowly and the reaction mixture is boiled for 2.5 hours, using reflux cooling. The reaction mixture is cooled to 0 °C, 12 ml 18% sodium-hydroxide solution is added to it in drops, and it is filtered. The filtrate is evaporated. We obtain raw 8-chloro-1,1-dimethyl 1,2,3,4,5,6-hexahydrobenzo[f]quinoline in the form of a yellow oil with complete yield, which is converted further immediately.

c) 10.6 g (0.043 mol) 8-chloro-1,1-dimethyl 1,2,3,4,5,6-hexahydrobenzo[f]quinoline and 6.6 ml (0.047 mol) triethyl amine are dissolved in 100 ml methylene chloride and a solution of 3.5 ml (0.047 mol) acetyl bromide in 20 ml methylene chloride is added in drops at 0 °C. The reaction mixture is extracted with methylene chloride and water after one hour of stirring and dried over magnesium sulphate and the solvent is distilled down in vacuum. After re-crystallization from a mixture of methylene chloride and hexane, we obtain 4-acetyl-8-chloro-1,1-dimethyl 1,2,3,4,5,6-hexahydrobenzo[f]quinoline in the form of white crystals with a melting point of 126-127 °C. Yield: 8.60 g (67%).

d) 5.30 g (0.018 mol) 4-acetyl-8-chloro-1,1-dimethyl 1,2,3,4,5,6-hexahydrobenzo[f]quinoline is dissolved in 100 ml methylene chloride and a suspension of 8.20 g (0.04 mol) m-chloro-perbenzoic acid (85%) in 50 ml methylene chloride is added to it in drops at 0 °C. The reaction mixture is stirred at room temperature for one and a half hours, then the precipitate that forms is filtered and extracted with methylene chloride and water. After chromatography performed on silicic-acid gel, elution with a 1:1 mixture of ethyl acetate and hexane, and re-crystallization from a mixture of ether and hexane, we obtain white [*sic*] 4-acetyl-11-chloro-7,7-dimethyl-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione melting at 113-115 °C. Yield: 2.50 g (42%).

e) 3 ml concentrated hydrochloric acid is added to a solution

of 2.40 g (0.008 mol) 4-acetyl-11-chloro-7,7-dimethyl 1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione and 150 ml methanol, and the reaction mixture is stirred for 24 hours at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down. The residue is chromatographed on silicic-acid gel, eluted with a 2:1 mixture of hexane and ethyl acetate, then chromatographed on aluminium oxide and eluted with ethyl acetate. We obtain 2-(4-acetamido-2,2-dimethyl-butyryl-5-chloro-hydrocinnamic-acid methyl ester in the form of a yellow oil. Yield: 1.65 g (63%).

Example 17

0.3 ml concentrated sulphuric acid is added to a solution of 10.00 g (0.032 mol) 2-(4-acetamidobutyryl)-5-chloro-cinnamic acid in 40 ml tetrahydrofurane in a steel autoclave and about 60 ml isobutylene is condensed in. The reaction mixture is stirred for 30 days at room temperature, the solution is evaporated, extracted with methylene chloride and water, and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on aluminium oxide, eluted with ethyl acetate, then chromatographed on silicic-acid gel and eluted with ethyl acetate. We obtain 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic-acid tertiary butyl ester in the form of a colourless oil. Yield: 0.8 g (7%).

Example 18

A mixture of 2.00 g (0.006 mol) 2-(4-acetamidobutyryl-5-chloro-cinnamic acid and 0.5 ml (0.006 mol) thionyl chloride in 20 ml methylene chloride is stirred for 5 minutes at room temperature, then a solution of 2,2-ml (0.023 mol) 3-hydroxymethyl) pyridine in 20 ml methylene chloride is added to it at 0 °C. The reaction mixture is stirred for one hour at room temperature, then the solution is evaporated. The residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on aluminium oxide and eluted with ethyl acetate. We obtain 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic-acid 3-pyridyl-methyl ester in the form of a drab oil, with complete yield. IR spectrum (film): 3288 m, 3074 m, 2936 m, 1736 m, 1684 s, 1656 s, 1591 m, 1558 s, 1236 m, 1205 m, 1158 m, 821 w.

Example 19

8.15 g (0.025 mol) 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic-acid methyl ester and 200 ml methanol-ammonia solution are stirred at room temperature for 30 hours. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is removed in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 9:1 mixture of chloroform and methanol, and re-crystallized from a mixture of methanol and ether. We obtain 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic-acid amide in the form of white crystals with a melting point of 149-151 °C. Yield: 2.90 g (37%).

Example 20

A mixture of 1.00 g (0.002 mol) 2-[4-(4-acetamidobutyramido)-butyryl]-5-chloro-hydrocinnamic-acid ethyl ester and 20 ml methanol-ammonia is stirred for 6 days at room temperature. The solution is evaporated, the residue is extracted with a mixture of methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on aluminium oxide, eluted with ethyl acetate, and re-crystallized from a mixture of methanol and tertiary butyl-methyl ether. We obtain 2-[4-(4-acetamidobutyramido)-butyryl]-5-chloro-hydrocinnamic-acid amide in the form of white crystals that melt at 126-127 °C. Yield: 0.48 g (48%).

Example 21

2.50 g (0.008 mol) 2-(acetamidobutyryl)-3-chloro-hydrocinnamic-acid methyl ester in 100 ml of a solution of methanol in water is stirred for 2 days at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. After re-crystallization from a mixture of methanol and ether, we obtain 2-(4-acetamidobutyryl)-3-chloro-hydrocinnamic-acid amide in the form of white crystals that melt at 148-150 °C. Yield: 1.70 g (72%).

Example 22

9.30 g (0.03 mol) 2-(4-acetamidobutyryl)-5-fluoro-hydrocinnamic-acid methyl ester in 200 ml of a solution of methanol in ammonia is stirred at room temperature for 6 days. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 20:1 mixture of methylene chloride and methanol, and re-crystallized from a mixture of methanol and ether. We obtain 2-(4-acetamidobutyryl)-5-fluoro-hydrocinnamic-acid amide in the form of white crystals that melt at 125-127 °C. Yield: 4.40 g (54%).

Example 23

A solution of 3.10 g (0.01 mol) 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid, 1.70 g (0.015 mol) 1,1'-carbonyl di-imidazole and 30 ml tetrahydrofurane is stirred at room temperature for one hour, then 1.1 ml (0.015 mol) diethyl amine is added to it at -70 °C and allowed to warm over one night. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel and eluted with ethyl acetate. We obtain 2-(4-acetamidobutyryl)-5-chloro-N,N-diethyl-hydrocinnamic-acid amide in the form of a yellow oil. Yield: 3.25 g (87%). IR spectrum (film): 3302 m, 1236 s, 1590 m, 1557 s, 1433 m, 1364 m, 1287 m, 1243 m, 1220 m, 1207 m, 1143 w, 1096 m, 1048 w, 985 w, 953 w, 894 w, 789 w.

Example 24

A solution of 3.10 g (0.01 mol) 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid and 1.70 g (0.011 mol) 1,1'-carbonyl di-imidazole in 30 ml tetrahydrofurane is stirred for one hour at room temperature, then 1.2 ml (0.011 mol) 1-methyl piperazine is added to it at -70 °C and allowed to warm over one night. The solution is evaporated, the residue is extracted first with methylene chloride and 2-N hydrochloric acid, then with methylene chloride and concentrated aqueous ammonium-hydroxide solution and dried over sodium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 20:1 mixture of methylene chloride and methanol, and crystallized from a mixture of ethyl acetate and

hexane. We obtain N-[3-[4-chloro-2-[2-[(4-methyl-piperazin-1-yl)-carbonyl)-benzoyl] acetamide in the form of white crystals that melt at 126-128 °C. Yield: 1.50 g (38%).

Example 25

A solution of 3.75 g (0.012 mol) 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid and 2.05 g (0.013 mol) 1,1'-carbonyl di-imidazole in 40 ml tetrahydrofurane is boiled for one hour, using reflux cooling, then 1.67 ml (0.013 mol) 2-piperidinoethyl amine is added to it. The reaction mixture is boiled for 2 hours while stirring, using reflux cooling, the residue is extracted with ethyl acetate and water (pH 14) and dried over sodium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid, eluted with a 4:2 mixture of chloroform and methanol, then chromatographed on aluminium oxide and eluted with a 98:2 mixture of ethyl acetate and methanol and finally crystallized from a mixture of ethyl acetate and cyclohexane. We obtain 2-(4-acetamidobutyryl)-5-chloro-N-(2-piperidinoethyl)-hydrocinnamic-acid amide in the form of white crystals that melt at 103-105 °C. Yield: 2.00 g (39%).

Example 26

A solution of 3.10 g (0.01 mol) 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid and 1.70 g (0.015 mol) 1,1'-carbonyl di-imidazole in 30 ml tetrahydrofurane is stirred for one hour at room temperature, then 1.35 g (0.015 mol) 2-phenyl-ethyl amine is added to it. The reaction mixture is stirred at room temperature for 2 hours, then the solution is evaporated. The residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. We obtain 2-(4-acetamidobutyryl)-5-chloro-N-phenyl-ethyl- hydrocinnamic-acid amide in the form of white crystals that melt at 127-128 °C. Yield: 3.20 g (75%).

Example 27

A mixture of 5.00g (0.016 mol) 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid, 1.26 g (0.013 mol) 4-aminopyridine, 4.16 g N,N'-dicyclohexyl carbo-di-imide, and 100 ml tetrahydrofurane is stirred at room temperature for 18 hours, then the solution is evaporated. The residue is extracted with ethyl acetate and water and dried over magnesium sulphate, and the solvent is removed in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 4:1 mixture of ethyl acetate and methanol, and crystallized from a mixture of methanol and tertiary butyl-methyl ether. We obtain 2-(4-acetamidobutyryl)-5-chloro-N-(2-pyridyl)-hydrocinnamic-acid amide in the form of white crystals that melt at 170-171 °C. Yield: 0.7 g (11%).

Example 28

A mixture of 2.00 g (0.006 mol) 2-(4-acetamidobutyryl*)-5-chloro-hydrocinnamic acid and 1.09 g (0.007 mol) 1,1'-carbonyl di-imidazole in 20 ml tetrahydrofurane is stirred for an hour and a half at room temperature, then 1.04 g (0.007 mol) L-alanine-ethyl-ester hydrochloride and 0.94 ml (0.008 mol) triethyl amine are added to it. The reaction mixture is stirred for 2 hours at room temperature, then extracted with a mixture of methylene chloride and water and dried over magnesium sulphate, and the solvent is removed in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 9:1 mixture of ethyl acetate and methanol, then chromatographed on aluminium oxide and eluted with ethyl acetate, and finally extracted with a mixture of ethyl acetate and hexane and dried over magnesium sulphate, and the solvent is removed in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 9:1 mixture of ethyl acetate and methanol, then chromatographed on aluminium oxide and eluted with ethyl acetate, and finally crystallized from a mixture of ethyl acetate and hexane. We obtain N-[2-(4-acetamidobutyryl)-5-chloro-hydrocinnamoyl]-L-alanine ethyl ester in the form of white crystals that melt at 106 °C. Yield: 0.85 g (32%).

[* *Hungarian 'acetamid' should be 'acetamido'*]

Example 29

A mixture of 3.10 g (0.01 mol) 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid and 1.70 g (0.015 mol) 1,1-carbonyl di-imidazole and 50 ml tetrahydrofurane is stirred at room temperature for one hour, then 2.51 g (0.011 mol) L-glutaminic-acid-diethyl-ester hydrochloride and 1.8 ml (0.011 mol) N-ethyl-di-isopropyl amine are added to it. The reaction mixture is stirred for 2 hours at room temperature, then the solution is evaporated. The residue is extracted with methylene chloride and water and dried over sodium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on aluminium oxide and eluted with a 97:3 mixture of methylene chloride and methanol and crystallized from a mixture of ethyl acetate and hexane. We obtain N-[2-(4-acetamidobutyryl)-5-chloro-hydrocinnamoyl]-L-glutaminic-acid diethyl-ether in the form of white crystals that melt at 109-111 °C. Yield: 2.45 g (50%).

Example 30

A mixture of 1.75 g (0.006 mol) 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid, 0.95 g (0.006 mol) 1,1-carbonyl di-imidazole, and 15 ml tetrahydrofurane is stirred at room temperature, then 1.0 ml (0.006 mol) N-ethyl-di-isopropyl amine and 0.82 g (0.006 mol) glycine ethyl ester hydrochloride are added to it. The reaction mixture is stirred at room temperature for one hour, then the solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on aluminium oxide, eluted with a 9:1 mixture of ethyl acetate and ethanol, then crystallized from a mixture of methylene chloride and tertiary butyl-methyl ether. We obtain N-[2-(4-acetamidobutyryl)-5-chloro-hydrocinnamoyl]-glycine ethyl ester in the form of white crystals that melt at 96 °C. Yield: 1.8 g (84%).

Example 31

3.00 g (0.008 mol) N-[2-(4-acetamidobutyryl)-5-chloro-hydroxy-cinnamoyl*]-glycine ethyl ester in a 30 ml methanol-ammonia solution is stirred at room temperature for 3 days. The solution is evaporated, the residue is extracted with methyhene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. We obtain 2-(4-acetamidobutyryl)-N-(carbamoyl-methyl)-5-chloro-hydrocinnamic-acid amide after re-crystallization of the residue from a mixture of methanol and tertiary butyl-methyl ether, in the form of white crystals that melt at 148-148 ° C. Yield: 2.80 g (complete).

[* *Hungarian 'hidroxcinnamoil' should be 'hidroxicinnamoil'*]

Example 32

0.38 g (0.1 mol) sodium-boron hydride is added to a solution

of 3.25 g (0.01 mol) 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic-acid methyl ester and 35 ml methanol, and the reaction mixture is stirred for one hour at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and water, then dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel and eluted with a 20:1 mixture of chloroform and methanol. We obtain 31 g (96%) 2-(4-acetamido-1-hydroxybutyl*)-5-chloro-hydrocinnamic-acid methyl ester in the form of a yellow oil. IR spectrum (film): 3306 m, 1735 s, 1653 s, 1596 m, 1555 s 1203 s, 1173 s, 1100 m, 826 w.
[* Hungarian "hldroxi" should be "hidroxi")

Example 33

A suspension of 15.5 g (0.05 mol) 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid and 8.50 g (0.052 mol) 1,1'-carbonyl di-imidazole in 350 ml tetrahydrofurane is stirred at room temperature for 2 hours, then 4.00 g (0.052 mol) glycolic-acid amide is added to it. The reaction mixture is stirred over one night at room temperature, then the solution is evaporated. The residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 20:1 mixture of methylene chloride and methanol and crystallized from a mixture of ethyl acetate and ether. We obtain 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic-acid carbamoyl-methyl ester in the form of white crystals that melt at 114-116 °C. Yield: 4.00 g (26%).

Example 34

A mixture of 3.10 g (0.01 mol) 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid, 1.70 g (0.01 mol) 1,1'-carbonyl di-imidazole, and 30 ml tetrahydrofurane is stirred for one hour at room temperature, then mixed with 2.50 g (0.01 mol) N-(2-aminoethyl)-5-chloro-2-pyridine-carboxyamide hydrochloride and 1.8 ml (0.01 mol) ethyl-di-isopropyl carboxyamide hydrochloride and 1.8 ml (0.01 mol) ethyl-di-isopropyl amine. The reaction mixture is evaporated after 2 hours, the residue is extracted with ethyl acetate and water and re-crystallized from a mixture of methanol and ether. The 2-(4-acetamidobutyryl)-5-chloro-N-[2-(5-chloro-2-pyridine-carboxamido)-ethyl hydrocinnamic-acid amide obtained melts at 163-165 °C. Yield: 3.30 g (67%).

Example 35

a) 8.00 g (0.06 mol) aluminium chloride is suspended in 600 ml methylene chloride, then mixed with a solution of 7.56 g (0.04 mol) 4-chlorophenyl-acetic-acid chloride and 20 ml methylene chloride at 0°C, and after that a solution of 4.17 g (0.04 mol) styrol and 400 ml methylene chloride is added to it at a temperature between -40 °C and -50 °C in drops. The reaction mixture is allowed to warm to room temperature then poured onto ice, extracted with methylene chloride, dried over magnesium sulphate and filtered through dicalite, and the solvent is removed in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 1:4 mixture of ethyl acetate and hexane, and re-crystallized from a mixture of ether and hexane. We obtain 6-chloro-3,4-dihydro-4-phenyl-2(1H)-naphthalene in the form of drab crystals that melt at 61-62 °C. Yield: 6.25 g (26%).

b) A solution of 73.3 g (0.23 mol) 6-chloro-3,4-dihydro-4-phenyl-2(1H)-naphthalinone and 1.5 litre toluene is mixed with a solution of 32.4 g (0.58 mol) potassium hydroxide and 83.7 g (0.64 mol) 3-(chloropropyl)-amine hydrochloride and the reaction mixture is heated for 42 hours, using reflux cooling. The reaction mixture is allowed to cool to room temperature, then 79 ml (0.56 mol) triethyl amine is added to it and a solution of 29.7 ml (0.42 mol) acetyl chloride in 250 ml toluene is added to it in drops. The reaction mixture is stirred for one hour then extracted with ethyl acetate and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel and eluted first with a 4:1 then with a 1:1 mixture of hexane and ethyl acetate, and finally it is re-crystallized from ethyl acetate. We obtain 4-acetyl-8-chloro-1,2,3,4,5,6-hexahydro-6-phenyl benzo[f]quinoline in the from of drab crystals that melt at 167-168 °C. Yield: 9.4 g (10%).

c) A solution of 8.13 g (0.04 mol) m-chloro-perbenzoic* acid in 80 ml methylene chloride (85%) is added to a solution of 6.60 g (0.02 mol) 4-acetyl-8-chloro-1,2,3,4,5,6-hexahydro-6-phenyl-benzo[f]quinoline and 70 ml methylene chloride. The reaction mixture is stirred for one hour at room temperature then filtered and extracted with methylene chloride and a saturated solution of sodium-bicarbonate, and dried over magnesium sulphate, and the solvent is distilled down in vacuum. We obtain 4-acetyl-11-chloro-1-phenyl-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione after crystallization of the residue from a mixture of methylene chloride and hexane, in the form of white crystals that melt at 184-185 °C. Yield: 4.30 g (60%).
[*Hungarian 'perbenzoesav' should be 'perbenzosav'*]

d) A solution of 3.30 g (0.009 mol) 4-acetyl-11-chloro-1-phenyl-1,2,4,5,6,7-hexahydro-4-benzazocine 3,8-dione, 40 ml tetrahydrofurane, and 20 ml 2-N hydrochloric acid is stirred for 2 days at room temperature, then the solution is evaporated. The residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel and eluted with a 1:1 mixture of hexane and ethyl acetate, and crystallized from a mixture of ethyl acetate and hexane. We obtain 2-(4-acetamidobutyryl)-5-chloro-β-phenyl-hydrocinnamic acid in the form of white crystals that melt at 114-116 °C. Yield: 2.5 g (72%).

Example 36

5.2 ml (0.005 mol) 1-N sodium-hydroxide solution is added to a suspension of 2.00 g (0.005 mol) 2-(4-acetamidobutyryl)-5-chloro-β-phenyl-hydrocinnamic acid and 120 ml water and mixed slowly with a solution of 0.88 g (0.005 mol) silver nitrate and 1 ml water, and the reaction mixture is stirred over one night at room temperature. The precipitate that forms is filtered, and mixed with 50 ml ethyl hodide* [**sic: Hungarian 'hodid' could be a misprint for 'klorid' or even 'iodid'*.] for 1 hour. The mixture is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down. The residue is chromatographed on silicic-acid gel and eluted with a 1:1 mixture of hexane and ethyl acetate, then chromatographed on aluminium oxide and eluted with a 1:1 mixture of hexane and ethyl acetate. We obtain 2-(4-acetamidobutyryl)-5-chloro-β-phenyl hydrocinnamic acid ethyl ester in the form of a colourless oil. Yield: 0.60 g (28%).

Example 37

120 ml 2-N hydrochloric acid is added to a solution of 23.8 g (0.06 mol) N-[3-[(11-chloro-2,3,5,6,7,8-hexahydro-3,8-dioxo-4-benzazocin-4(1H)-yl)-carbonyl] propyl] acetamide and 240 ml tetrahydrofurane and it is stirred for 8 days at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium

sulphate, and the residue is distilled down in vacuum. After re-crystallization from a mixture of methanol and ether, we obtain 2-[4-(4-acetamidobutyramido)-butyryl]-5-chloro-hydrocinnamic acid in the form of drab crystals that melt at 108 °C. Yield: 21.3 g (85%, raw product).

Example 38

A mixture of 6.00 g (0.015 mol) 2-[4-(4-acetamidobutyramido)-butyryl]-5-chloro-hydrocinnamic acid, 2.57 g (0.016 mol) 1,1'-carbonyl di-imidazole and 60 ml tetrahydrofurane is stirred for an hour and a half at room temperature, then 2.22 g (0.016 mol) glycine-ethyl-ester hydrochloride and 2.2 ml (0.016 mol) triethyl amine are added to it. The reaction mixture is stirred at room temperature for one hour, then the solution is evaporated, extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 9:1 mixture of ethyl acetate and ethanol, and crystallized from a mixture of methanol and ether. We obtain N-[2-([4-(4-acetamidobutyramido)-butyryl]-5-chloro-hydrocinnamoyl]-glycine ethyl ester in the form of white crystals that melt at 94-96 °C. Yield: 4.20 g (58%).

Example 39

A solution of 2.50 g (0.005 mol) N-[2-[4-(4-acetamidobutyramido)-butyryl]-5-chloro-hydrocinnamoyl]-glycine ethyl ether in 50 ml of a methanol-ammonia solution is stirred over one night at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. After re-crystallization twice from a mixture of methanol and ether, we obtain 2-[4-(4-acetamidobutyramido)-butyryl]-N-(carbamoyl-methyl)-5-chloro-hydrocinnamic acid amide. The melting point of the white crystals is 172-174 °C. Yield: 0.90 g (38%).

Example 40

15 ml 2-N sodium-hydroxide solution is added to a solution of 1.50 g (0.004 mol) N-[2-(4-acetamidobutyryl)-5-chloro-hydrocinnamoyl]-glycine ethyl ester and 15 ml tetrahydrofurane, and the reaction mixture is stirred for one hour at room temperature. The reaction mixture is acidified with 17 ml 2-N hydrochloric acid, extracted with ethyl acetate and water, then the solvent is removed in vacuum. After re-crystallization of the residue from a mixture of ethyl acetate and ether, we obtain N-[2-(acetamido-butyryl)-5-chloro-hydrocinnamoyl]-glycone in the form of white crystals that melt at 88-89 °C. Yield: 0.9 g (65%).

Example 41

a) 25.0 g (0.115 mol) 8-chloro-1,2,3,4,5,6-hexahydrobenzo[f]quinoline is dissolved in 145 ml methylene chloride, then 21.8 g (0.182 mol) of a solution of α-chloroacetyl isocyanate in 30 ml methylene chloride is added to it in drops and the reaction mixture is stirred over one night at room temperature. 200 ml methanol is added to the reaction mixture, and it is stirred for another 24 hours. The 8-chloro-N-(chloroacetyl)-2,3,5,6-tetrahydrobenzo[f]quinoline-4(1H)-carboxamide is filtered. After the product is re-crystallized from a mixture of ethyl acetate and ether, it melts at 158-161 °C. An additional quantity of product is obtained from the filtrate and the mother lye. Yield: 16.9 g (61%).

b) A suspension of 11.85 g (0.035 mol) 8-chloro-N-(chloroacetyl)-2,3,5,6-tetrahydrobenzo[f]quinoline-4(1H) carboxamide and 4.4 ml (0.091 mol) hydrazine hydrate in ethanol is stirred at room temperature for 3 hours, then the reaction mixture is evaporated in vacuum and the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The 8-chloro-2,3,5,6-tetrahydro-benzo[f]quinine 4(1H)-carboxyamide methylene-chloride obtained after re-crystallization with methylene chloride melts at 169-171 °C. Yield: 9.2 g (complete).

c) 9.20 g (0.035 mol) 8-chloro-2,3,5,6-tetrahydro-benzo[f]quinoline-4(1H)-carboxamide is suspended in 100 ml methylene chloride, then a solution of 14.1 g (0.071 mol) m-chloro-perbenzoic acid (85%) in 150 ml methylene chloride is added to it in drops at 10-15°C. The reaction mixture is stirred for an hour and a half at room temperature, then it is poured into a saturated solution of sodium bicarbonate, extracted with methylene chloride, dried over magnesium sulphate, and the solvent is distilled down in vacuum. The solid matter obtained is washed with hot ethyl acetate. After re-crystallization from a mixture of dioxane and ether, we obtain 11-chloro-2,3,5,6,7,8-hexahydro-3,8-dioxo-4- benzazocine-4(1H)-carboxamide in the form of white crystals that melt at 182-184 °C. Yield: 8.05 g (78%).

d) 7 ml concentrated hydrochloric acid is added to a solution of 6.80 g (0.023 mol) 11-chloro-2,3,5,6,7,8-hexahydro-3,8-dioxo-4-benzazocine-4(1H)-carboxamide with 5 l ethanol, and the reaction mixture is stirred for 13 days at room temperature. The solution is evaporated, the residue is extracted with methylene chloride and water and dried over magnesium sulphate, and the solvent is distilled down in vacuum. The residue is chromatographed on silicic-acid gel, eluted with a 97:3 mixture of methylene chloride and methanol, and after this it is re-crystallized from a mixture of ethyl acetate and hexane. We obtain 5-chloro-2-(4-carbamidobutyryl)-hydrocinnamic acid ethyl ester. Yield: 4.20-g (53%).

Example 42

Tablets of the following composition are prepared containing N-[2-(4-acetamidobutyryl)-5-chloro-hydrocinnamoyl]-glycine ethyl ester:

Component:	Quantity, mg/tablet
1. Active ingredient (micronized)	50 mg
2. Milk sugar	120 mg
3. Corn starch	50 mg
4. Poly(vinyl-pyrrolidone)	8 mg
5. Sodium-carboxymethyl starch	20 mg
6. Magnesium stearate	2 mg
Total weight: 250 mg	

The active ingredient, the milk sugar, and corn starch are mixed together into a homogeneous mixture. The mixture is sifted and moistened with aqueous poly(vinyl-pyrrolidone) solution, granulated, and dried. The dried granulate is mixed together with the sodium-carboxymethyl starch and mixed together with magnesium stearate, and the mixture obtained is pressed into tablets of appropriate size with breaking edges [*sic*].

Example 43

Tablets of the following composition are prepared containing N-[2-(4-acetamidobutyryl)-5-chloro-hydrocinnamoyl]-glycine ethyl ester as the active ingredient.

Component	Quantity, mg/tablet
1. Active ingredient (micronized)	10 mg

2. Milk sugar	88 mg
3. Microcrystalline cellulose	60 mg
4. Corn starch	20 mg
5. Sodium-carboxymethyl starch	20 mg
6. Magnesium stearate	2 mg

Total weight: 200 mg

The active ingredient is mixed homogeneously with the milk sugar, then sifted. After this, a mixture of the microcrystalline cellulose, corn starch, and sodium-carboxymethyl starch is added, then the magnesium stearate is mixed in. From the mixture, which is ready for pressing, tablets are prepared with appropriate breaking edges [*sic*] are prepared.

Example 44

Tablets of the following composition are prepared containing N–[2-(4-acetamidobutyryl)-5-chloro-hydrocinnamoyl]-glycine ethyl ester as the active ingredient.

Component	Quantity, mg/tablet
1. Active ingredient (micronized)	0.10 mg
2. Milk sugar	126.90 mg
3. Corn starch	50.00 mg
4. Poly(vinyl- pyrrolidone)	6.00 mg
5. Sodium-carboxymethyl starch	15.00 mg
6. Magnesium stearate	2.00 mg

Total weight: 200.00 g

The active ingredient, the milk sugar, and the corn starch are mixed together homogeneously, The mixture obtained is moistened with aqueous poly(vinyl-pyrrolidone) solution, granulated, and dried. The dried granules are mixed together with the sodium-carboxymethyl starch and the magnesium stearate, and the mixture obtained is pressed into tablets of appropriate size with breaking edges [*sic*].

Patent claims

1. A procedure[for producing] hydrocinnamic acid derivatives of general formula (I)
((in which formula,
among R^1, R^2, R^3 and R^4, one or two represent a halogen atom or a methoxy group and the others represent a hydrogen atom;
R^5 is a hydrogen atom or a phenyl group,
R^6 is a group of general formula
$-OR^{12}$ (a) or $-NR^{13}R^{14}$ (b),
R^7 is an alkyl group with 1-4 carbon atoms, an alkanoyl-amino-(alkyl group with 2-5 carbon atoms) group, an amino group or an alkoxy-phenyl group with 1-4 carbon atoms,
R^8 and R^9 is a hydrogen atom or an alkyl group with 1-4 carbon atoms,
R^{10} and R^{11} together is an oxo group,
R^{12} is a hydrogen atom, an alkyl group with 1-10 carbon atoms, a pyridyl-methyl or carbamoyl-methyl group,
R^{13} is a hydrogen atom or an alkyl group with 1-4 carbon atoms,
R^{14} is a hydrogen atom, an alkyl group with 1-4 carbon atoms, a pyridyl group, a phenyl-(alkyl group with 1-4 carbon atoms) group, a carboxy-(alkyl group with 1-4 carbon atoms) group, a carbamoyl-(alkyl group with 1-4 carbon atoms) group, a di*-(alkoxy-group with 1-4 carbon atoms-(carbonyl-)alkyl group with 2-5 carbon atoms) group, a piperidino-(alkyl group with 2-4 carbon atoms) group or a halogen-pyridinocarboxamido-(alkyl group with 2-4 carbon atoms) or
[* Hungarian "d" should be "di"]
R^{13} and R^{14}, together with an adjacent nitrogen atom to which they are attached, form a 4-(alkyl group with 1-4 carbon atoms)-piperazin-1-yl group,
where the heterocyclic groups at R^{12} and R^{14} are connected through one of their carbon atoms)),
containing an $-OR^{12}$ group of general formula (a) in the R^6 position, a hydrogen atom or an alkyl group of 1-10 carbon atoms in the R^{12} position, and an oxo group in the position of R^{10} and R^{11} together, a benzazocine dione of general formula (II) (in which formula R^1, R^2, R^3, R^4, R^5, R^7, R^8 and R^9 is as given above) is treated with acid in the presence of a compound of general formula (III) (in which formula $R^{12'}$ is a hydrogen atom or an alkyl group of 1-10 carbon atoms) , then, if desired, the compound of general formula (I) obtained is subjected to one or more of the following conversions:

(i) a compound of general formula (a) in the R^6 position or a reactive derivative thereof – preferably an acid halogenated, an imidazolide or a silver salt – is converted by esterification into a compound of general formula (I) in which R^6 is a group of general formula (a) and R^{12} has a meaning other than a hydrogen atom,

(ii) a compound of general formula (I) containing a group of general formula (a) in the R^6 position and a hydrogen atom in the R^{12} position or a reactive derivative thereof – preferably an ester or imidazole thereof – is reacted with a compound of general formula (IV) (in which formula R^{13} is as given above and $R^{14'}$ is as given above for R^{14}, but it cannot represent a carboxy-(alkyl group with 1-4 carbon atoms) group) or a group of general formula (b) in the R^6 position and a compound of general formula (I) containing a carboxy-(alkyl group with 1-4 carbon atoms) group in the R^{14} position or a reactive derivative thereof is brought into a reaction with ammonia,

(iii) a compound of general formula (I) in which R^{10} and R^{11} together form an oxo group is reduced – preferably with a complex hydride, especially preferably with sodium-boron hydride or

(iv) a compound of general formula (I) containing a group of general formula (b) in the R^6 position and an alkoxy(-carbonyl-group with 1-4 carbon atoms)-alkyl group with 1-4 carbon atoms is hydrolyzed into a compound of general formula (I) containing a carboxy-(alkyl group with 1-4 carbon atoms) group in the R^{14} position.

2. The procedure according to claim 1 for producing a compound of general formula (I) containing a hydrogen atom at the R^4 position, a chlorine atom at the R^1 position, and a hydrogen atom at the R^2 and R^3 positions or a hydrogen atom at the R^1 position and a chlorine atom at the R^2 and R^3 positions, or a hydrogen atom at the R^1 and R^2 positions and a fluorine atom, chlorine atom, or methoxy group at the R^3 position, characterised in that the appropriate starting materials are used.

3. The procedure according to claim 2 for producing a compound of general formula (I) containing a chlorine atom at the R^3 position, and a hydrogen atom at the R^1, R^2 and R^4 positions, characterised in that the appropriate starting materials are used.

4. A procedure according to any of claims 1-3 for producing compounds of general formula (I) containing a hydrogen atom at the R^5 position, characterised in that the appropriate starting materials are used.

5. A procedure according to any of claims 1-4

for producing compounds of general formula (1), in which R^6 is a group of general formula (a) or (b) as defined in claim 1, R^{12} is a hydrogen atom, a methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary-butyl, n-nonyl, 5-nonyl, 3-pyridyl-methyl, or carbamoyl-methyl group, and R^{13} and R^{14} have the same meaning and both represent a hydrogen atom or an ethyl group or R^{13} and R^{14}, together with the adjacent nitrogen atom to which they are attached form a 4-methyl-piperazin-1-yl group or R^{13} is a hydrogen atom and R^{14} is a 4-pyridyl, 2-phenyl-ethyl, 2-piperidinoethyl, carboxymethyl, ethoxycarbonyl-methyl, carbamoyl-methyl, 1-ethoxycarbonyl-ethyl, 1,4-bis-(ethoxycarbonyl)-2-butyl or 2-(5-chloro-2-pyridinocarboxyamido)-ethyl group, characterised in that the appropriate starting materials are used.

6. A procedure for producing compounds of general formula (I) according to claim 5, in which R^{12} is an ethyl, n-propyl, isopropyl, n-nonyl, or carbamoyl-methyl group, the meaning of R^{13} is a hydrogen atom, and R^{14} represents a hydrogen atom, ethyoxycarbonyl-methyl or 1,4-bis-(ethoxycarbonyl)-2-butyl group, characterised in that the appropriate starting materials are used.

7. A procedure according to any of claims 1-6 for producing compounds of general formula (I) containing a methyl, 3-acetyl-aminopropyl, amino or p-methoxyphenyl group in the R^7 position, characterised in that the appropriate starting materials are used.

8. A procedure according claim 7 for producing compounds of general formula (I) containing a methyl or 3-acetyl-aminopropyl group in the R^7 position, characterised in that the appropriate starting materials are used.

9. A procedure according to any of claims 1-8 for producing compounds of general formula (I), in which R^8 and R^9 have the same meaning and both represent a hydrogen atom or a methyl group, characterised in that the appropriate starting materials are used.

10. A procedure according to claim 9 for producing compounds of general formula (I) containing hydrogen atoms at the R^8 and R^9 positions, characterised in that the appropriate starting materials are used.

11. A procedure according to claim 1-10 for producing compounds of general formula (I) containing an oxy-group in the R^{10} and R^{11} positions together, characterised in that the appropriate starting materials are used.

12. A procedure according to claim 1 for producing N–[2-(4-acetamidobutyryl)-5-chloro-hydrocinnamoyl] glycine ethyl ester, characterised in that the appropriate starting materials are used.

[*claim 13 missing*]

14. A procedure according to claim 1 for producing [2-(4-acetamidobutyramido)-butyryl] 5-chloro-hydrocinnamic acid amide, characterised in that the appropriate starting materials are used.

15. A procedure according to claim 1 for producing [2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid isopropyl ester, characterised in that the appropriate starting materials are used.

16. A procedure according to claim 1 for producing [2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid ethyl ester, characterised in that the appropriate starting materials are used.

17. A procedure according to claim 1 for producing [2-(4-acetamidobutyryl)-5-chloro-hydrocinnamoyl]-L-glutaminic-acid diethyl ester, characterised in that the appropriate starting materials are used.

18. A procedure according to claim 1 for producing [2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid methyl ester characterised in that the appropriate starting materials are used.

19. A procedure according to claim 1, characterised in that the appropriate starting materials are used.

20. A procedure according to claim 1 for producing 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid propyl ester, characterised in that the appropriate starting materials are used.

21. A procedure according to claim 1 for producing 2-(4-acetamidobutyryl)-N–(carbamoyl-methyl)-5-chloro-hydrocinnamic acid, characterised in that the appropriate starting materials are used.

22. A procedure according to claim 1 for producing 2-(4-acetamidobutyryl)-5-chloro-hydrocinnamic acid nonyl ester characterised in that the appropriate starting materials are used.

23. A procedure for producing pharmaceutical preparations – especially for treating and preventing brain insufficiency and that can be used to improve cognitive functions –, characterised in that a compound of general formula (I) according to claim 1 and, if desired, one or more pharmaceutical agents, are mixed with inert pharmaceutical excipients and brought into a galenic form.

3 drawings

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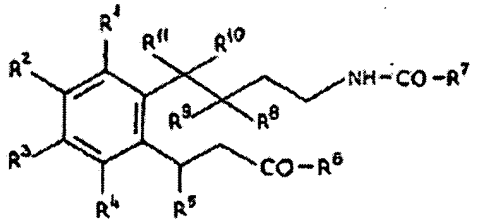
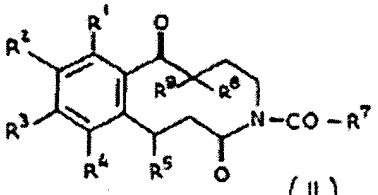


(I)



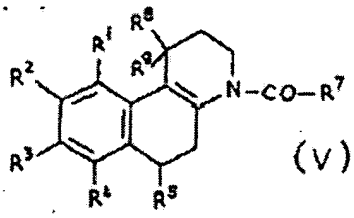
(II)

$HOR^{12'}$

(III)

$HNR^{13}\ R^{14'}$

(IV)



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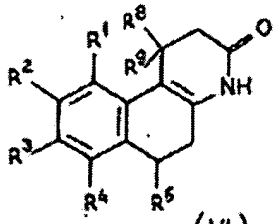

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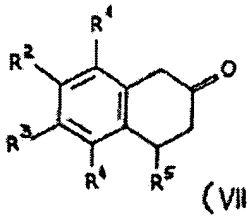
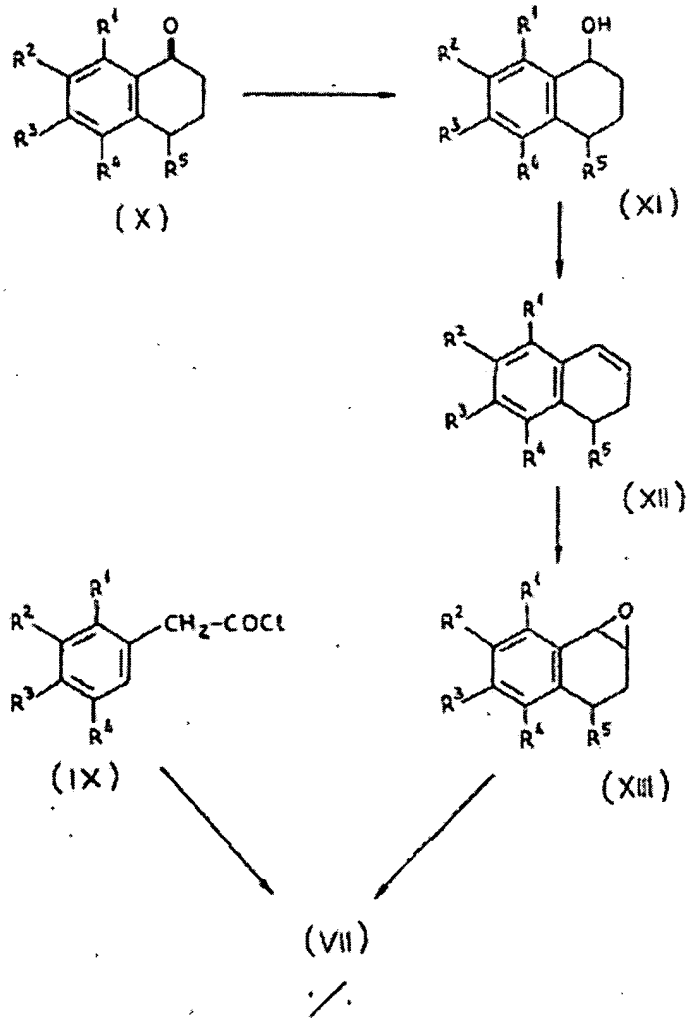


(VII)

$X-(CH_2)_3-NH_2$ (VIII)

Reaction diagram A



(continued)

Reaction diagram A (continued)